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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/622,492	07/21/2003	Karen Jackson	330499.00009	4987
27160 7590 03/09/2007 PATENT ADMINISTRATOR KATTEN MUCHIN ROSENMAN LLP 1025 THOMAS JEFFERSON STREET, N.W. EAST LOBBY: SUITE 700 WASHINGTON, DC 20007-5201			EXAMINER ANDERSON, JAMES D	
			ART UNIT	PAPER NUMBER
			1614	
SHORTENED STATUTORY PERIOD OF RESPONSE		MAIL DATE	DELIVERY MODE	
3 MONTHS		03/09/2007	PAPER	

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No. 10/622,492	Applicant(s) JACKSON, KAREN	
	Examiner James D. Anderson	Art Unit 1614	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 08 February 2007.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1,2,5,8-38,40,41 and 46 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1,2,5,8-38,40,41 and 46 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08)
Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

Applicant's arguments, filed 2/8/2007, have been fully considered but they are not deemed to be persuasive. Rejections and/or objections not reiterated from previous Office Actions are hereby withdrawn. The following rejections and/or objections are either reiterated or newly applied. They constitute the complete set presently being applied to the instant application.

Status of the Claims

Claims 1-2, 5, 8-38, 40-41 and 46 are currently pending and are the subject of this Office Action. Claims 1, 5 and 24 are presently amended and claim 46 is newly presented.

Response to Arguments

Applicant's arguments filed 2/8/2007 have been fully considered but they are not persuasive. Firstly, applicant argues that Panos (WO 99/18967) does not teach or reasonably suggest that devazepide itself can act to enable the overall dose of the opioid to be reduced or minimized, concurrent with improved analgesia. Panos discloses pharmaceutical formulations for treating chronic and neuropathic pain comprising an opioid-potentiating amount of a CCK antagonist and an analgesic amount (*i.e.* a therapeutically effective amount) of an opioid (Abstract). A "potentiating amount" is an amount that leads to greater opioid effect (*i.e.* analgesia) than the analgesia observed when opioid is administered alone. One skilled in the art would clearly recognize that if a CCK antagonist potentiates (*i.e.* increases) the effect of a given dose of opioid, said dose of opioid could be reduced while still maintaining an analgesic effect.

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Further, the invention of Panos is based on the thesis that “blockage of CCK action may be an effective supplement to morphine (or other opioid) administration in the treatment of chronic pain” (page 1, lines 28-30). Thus, Panos clearly provides one skilled in the art with the motivation to co-administer a CCK antagonist and an opioid. Secondly, applicant argues that Panos teaches away from the claimed invention by teaching that a “fixed” dosage preparation of devazepide and an opioid is necessary in order to potentiate the analgesic effect of the opioid. This argument is not persuasive because optimization of dosage is well within the level of ordinary skill in the art and Panos clearly teaches that different ratios of CCK antagonist to opioid may be used. Panos discloses that components are preferably present in a ratio of 1:2 to 1:40 (CCK antagonist to opioid) (page 5, lines 11-12). Thirdly, applicant argues that Panos teaches that devazepide has no intrinsic analgesic properties. It is not clear how this relates to the instant rejections because this is not being claimed. Further, nowhere does examiner maintain that devazepide has analgesic properties when administered alone. Finally, applicant argues that Panos only teaches that morphine analgesia is enhanced by devazepide when either is given as a single dose over a two-hour period. “There are no data for long term or ‘regular’ dosing or data showing that the observed effects are simply transient or if they are sustainable.” See Applicant’s Arguments at page 10. This argument is not persuasive because the instant rejections are based on the obviousness of the claimed invention. The optimization of dosing, dosing schedules, etc. taught by the prior art would have been *prima facie* obvious in view of the combined disclosures.

In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on

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combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). In the instant case, applicant has only presented arguments with respect to the Panos reference. All 35 U.S.C. § 103(a) rejections set forth in the previous Office Action were based on a combination of references. As such, applicant's arguments are *prima facie* unpersuasive because they have not addressed the teachings of any reference other than the Panos reference.

The 35 U.S.C. § 103 rejections are maintained and reiterated below. In addition, applicant's amendments necessitated new grounds of rejection under 35 U.S.C. § 112, 1st and 2nd Paragraphs.

Claim Rejections - 35 USC § 112 (1st Paragraph)

The following is a quotation of the first paragraph of 35 U.S.C. § 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-2, 5, 8-38, 40-41 and 46 are rejected under 35 U.S.C. § 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a New Matter rejection.

In the instant case, claim 1 has been amended to recite the limitation wherein upon subsequent treatments “over a period of at least 5 weeks” the amount of opioid is reduced. Applicant points to ¶ [0034], second sentence as providing support for this limitation. However,

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the treatment schedule in Table 1 of the specification indicates that “subsequent treatments” occur for: 2 weeks (Treatment 1) followed by a washout of 4-21 days; 2 weeks (Treatment 2) followed by a washout of 4-21 days; and 2 weeks (Treatment 3). This does not provide support for the limitation “over a period of at least 5 weeks” as instantly claimed. The “subsequent treatments” shown in Table 1 total a period of *at least* 8 weeks (2 weeks + 4 days + 2 weeks + 4 days + 2 weeks).

In addition, claim 1 has been amended to recite the limitation “regularly administering to the patient a therapeutically effective amount of the opioid and a potentiating amount of devazepide”. This limitation implies that the opioid and devazepide are being administered according to some “regular” undefined schedule. Applicant points to ¶ [0032], first sentence as providing support for this limitation. However, this section of the specification only states that during pre-treatment, “patients continued to take regular doses of strong opioids and break-through analgesics when required”. Thus, the specification does not provide support for the limitation “regularly administering to the patient a therapeutically effective amount of the opioid and a potentiating amount of devazepide” as instantly claimed. A “regular dose” indicates a normal or typical dose, not a regular *schedule*. Further, the specification indicates that the “regular doses” are taken *when required*, not on a predetermined schedule.

Claim Rejections - 35 USC § 112 (2nd Paragraph)

The following is a quotation of the second paragraph of 35 U.S.C. § 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

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Claims 1-2, 5, 8-38, 40-41 and 46 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. In the instant case, claim 1 has been amended to recite the limitation “regularly” in line 3. This limitation is indefinite because it is subjective. It is not clear what schedule of administration applicant intends the term “regularly” to encompass. Is it applicant’s intent that “regularly” mean hourly? Daily? Monthly? Yearly? The metes and bounds of this claim limitation are not clear and concise as required by 35 U.S.C. § 112, 2nd Paragraph.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. § 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

Claims 1-2, 5, 8-9, 12-24, 27-32, 36-38, 40-41 and 46 are rejected under 35 U.S.C. § 103(a) as being unpatentable over WO 99/18967 (prior art of record), hereinafter “WO”, in view of Dourish *et al.* (prior art of record).

The instant claims are drawn to a method of reducing the amount of an opioid (from 25 to 95%) administered to a patient comprising “regularly” administering an opioid and a potentiating amount of devazepide. In order to establish a *prima facie* case of obviousness, the prior art must provide the skilled artisan with the motivation to reduce the amount of opioid when it is administered with devazepide.

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WO discloses pharmaceutical formulations for treating chronic and neuropathic pain comprising an opioid-potentiating amount of a CCK antagonist and an analgesic amount (*i.e.* a therapeutically effective amount) of an opioid (Abstract). The reference provides the skilled artisan with the motivation to administer a CCK antagonist and an opioid together as well as the motivation to reduce the amount of opioid administered to a patient. The authors disclose that (emphasis added):

“CCK also appears to play a role in the development of tolerance to opioid analgesia as blockade of CCK receptors has been shown to prevent tolerance to morphine. Hence, blockade of CCK receptors by CCK antagonists may reverse or prevent the development of opiate tolerance in patients, and also potentiates the analgesic effects of opioids”. WO, page 1, lines 23-27.

There is evidence that exogenous CCK attenuates analgesia induced by morphine or release of endogenous opioids (page 1, lines 18-20). The invention of WO is based on the thesis that “blockage of CCK action may be an effective supplement to morphine (or other opioid) administration in the treatment of chronic pain” (page 1, lines 28-30). The formulations disclosed in the reference also comprise a biphasic carrier (page 2, lines 21-28). The components are preferably present in a ratio of 1:2 to 1:40 (CCK antagonist to opioid) (page 5, lines 11-12). The opiate drug includes the opioids recited in instant claim 8 (page 5, lines 13-20) and the CCK antagonist is preferably devazepide (page 6, lines 5-6). The formulations are preferably solid formulations, including tablets (page 7, lines 11-14). Preferable daily doses of the CCK antagonist are in the range of 0.5 to 300 mg per day (page 7, lines 30-31) and, for devazepide, preferably 1-10 mg/day (5-10 mg/day orally or 1-3 mg/day *i.v.*) (page 8, lines 1-2).¹

¹ The average human weighs approximately 71 kg. Thus, the ranges disclosed in the WO reference are equivalent to 0.07 to 0.14 mg/kg/day (oral) and 14 to 42 µg/kg/day (*i.v.*).

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Intravenous emulsions, infusions and coated S.R. tablets are disclosed (pages 8-11). The intravenous infusion of Example 2 includes 0.015 g MK-329 (devazepide) in 1000 mL and it is stated, "one litre of emulsion may be administered intravenously over a 24-hour period" (page 9, lines 5-21). This amounts to 0.211 mg/kg/day devazepide through intravenous administration (average human weight of 71 kg), thus meeting the limitations of instant claim 32.

Dourish discloses that the CCK antagonist devazepide potentiates the amount of opioid administered to rats in the tail withdrawal procedure (Abstract, Fig. 2a, Fig. 4). The Dourish reference also provides the motivation to reduce to the amount of opioid administered wherein the authors conclude that:

"[T]he data suggests that devazepide may have therapeutic utility as an adjuvant to morphine analgesia allowing lower doses of the opiate to be used to relieve pain and reducing the risk of opiate-induced respiratory depression" (Abstract).

Devazepide was administered by *i.p.* injection in doses ranging from 1 to 300 µg/kg (Fig. 2a) as well as by *p.o.* administration in doses of 3 to 30 µg/kg (Fig. 4) thus teaching the limitations of claims 27-30. Figure 1 (page 1160) demonstrates the analgesic effect of morphine in the tail withdrawal latencies in the squirrel monkey tail withdrawal test. It is clear from this figure that a dose of morphine above 0.1 mg/kg is required to induce an analgesic effect. Devazepide, when administered alone, induced no analgesia (Fig. 2a, page 1161). However, morphine analgesia was enhanced by *i.p.* injection of devazepide in the squirrel monkey tail withdrawal test (Fig. 2a and Fig. 4). In these tests, 0.1 mg/kg of morphine was administered after administration of devazepide. The amount of morphine administered (0.1 mg/kg) did not induce analgesia when administered alone (Fig. 1). Thus, it is clear from the data that

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devazepide allows a reduction in the amount of opioid required to induce analgesia when compared to opioid-induced analgesia in the absence of devazepide.

Given the disclosures of Dourish and WO, the instant claims would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made. The motivation to combine the references is found in WO wherein it is disclosed that there is evidence that blockage of CCK action may be an effective supplement to morphine. WO also provides the motivation to reduce the amount of opioid administered to a patient (e.g. patients develop tolerance to opioids). In addition, Dourish demonstrates the potentiating effects of devazepide on morphine-induced analgesia. Pharmaceutical formulations of opioids and devazepide, in the ratios and dosages instantly claimed, were known in the art. It was also known that devazepide potentiates the analgesic effect of morphine. Examiner maintains that Dourish clearly demonstrates this to be the case. Thus, the skilled artisan would be imbued with at least a reasonable expectation that a lower dose of opioid could be administered to a patient in need thereof if the opioid were administered with a potentiating amount of devazepide.

Claims 10-11, 25-26 and 33-35 are rejected under 35 U.S.C. § 103(a) as being unpatentable over WO 99/18967 and Dourish *et al.* as applied to claims 1-2, 5, 8-9, 12-24, 27-32, 36-38, 40-41 and 46 above, and further in view of U.S. Patent No. 6,103,261 (Issued August 15, 2000) and Caplan *et al.* (JAMA, 1989, vol. 261, Abstract).

WO and Dourish disclose as above. The '261 patent is provided as evidence that the instantly claimed dosages of opioid were known in the art. For example, '261 discloses oral dosage forms of an opioid analgesic comprising from 15 to 800 mg morphine (column 4, lines

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51-54) or 10 to 400 mg oxycodone (col. 4, lines 55-59) thus teaching the limitations of claims 10 and 33-35.

The Caplan reference is provided as evidence that transdermal administration of the opioid, fentanyl, was known in the art. The safety and efficacy of transdermal fentanyl citrate for postoperative pain management demonstrated that this administration route is safe and effective for treating pain (Abstract) thus teaching the limitations of claims 11 and 25-26. Thus, the instantly claimed doses and methods of administering opioids would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

Conclusion

No claims are allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

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Any inquiry concerning this communication or earlier communications from the examiner should be directed to James D. Anderson whose telephone number is 571-272-9038. The examiner can normally be reached on MON-FRI 9:00 am - 5:00 pm EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin Marschel can be reached on 571-272-0718. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.



James D. Anderson, Ph.D.
Patent Examiner
AU 1614

February 28, 2007



**PHYLLIS SPIVACK
PRIMARY EXAMINER**